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The Dual Risk Approach in Nutrition: Present and Future Perspectives and Challenges

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THE DUAL RISK APPROACH IN NUTRITION

PRESENT AND FUTURE PERSPECTIVES AND CHALLENGES

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Inge Tetens, Hanna Eneroth, Helle Margrete Meltzer,
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Preface

Nordic co-operation is one of the world's most extensive forms of regional collaboration, involving, Denmark, Finland, Iceland, Norway, and Sweden. Nordic co-operation has firm traditions in politics, economics, and culture and plays an important role in the European and international collaboration. Nordic co-operation is built on common values and a willingness to achieve results that contribute to the development of a strong Nordic community in a strong Europe. The Nordic co-operation also aims at creating competencies and competitiveness in the global community.

Nordic co-operation in nutrition has a long history with the main initial objective to determine the level of nutrient intake that would prevent nutrient deficiency disorders. Later, with the recognition of the needs to develop nutrient reference values that address optimal levels of nutrient intakes in relation to non-communicable diseases (NCDs) along with values to reduce the risk of toxic nutrient intakes, the Nordic countries developed a set of reference values, the Nordic Nutrition Recommendations.

The Nordic Council of Ministers supports the task of setting the common Nordic Nutrition Recommendations, which have become a key document in the Nordic food-nutrition-health area and related activities. The regional scientific forces have resulted in an overall Nordic action plan for "A Better Life through Diet and Physical Activity" and other activities. Along with the development of the nutrition sciences, the framework for developing nutrition reference values, and the increasing amounts of data available, it is relevant constantly to address the principles, the approaches, and the optimal use of the expertise and knowledge.

The Nordic Council of Ministers provided funds through a grant from the Nordic Working Group for Diet, Food and Toxicology (NKMT) to a Project Team from the five Nordic countries: Inge Tetens, Professor, DK (project leader); Inga Thorsdoittir, Professor, IS; Liisa Valsta, Senior Scientist, FI, Hanna Eneroth, Risk-Benefit Assessor, Nutritionist and PhD, SE. The group discussed the current dual risk assessment approach in nutrition, including the practices, challenges and perspectives in relation to the setting of dietary reference values in the Nordic Nutrition Recommendations. To strengthen the Nordic capacity in the area and to enhance the transparency on pertinent issues, a Nordic symposium was held with invited guest experts and a broader audience. The symposium was hosted by "Vitality – Centre for good older lives" and Faculty of Science, University of Copenhagen. The present report summarizes this symposium.

Summary

Nordic co-operation in the area of nutrition has a long history that includes the development and updates of the Nordic Nutrition Recommendations. As part of this continuous work, a Nordic project team organized with financial support from the NKMT a symposium on the dual risk approaches in nutrition.

The purpose of the symposium was to discuss the current use and some of the challenges in applying a nutrition risk assessment approach in setting nutrition recommendations in the light of the forthcoming update of the Nordic Nutrition Recommendations (NNR).

As the first speaker Inga Thorsdottir, IS reminded that the concept of a dual risk approach in nutrition stemmed from the potential risk of insufficient nutrient intakes at the low end and of toxic nutrient intakes at the upper end of the intake distribution range. The development of the NNR through the last almost 40 years reflects the increased awareness that a single figure of nutrient average requirement is insufficient to cover the variety of needs for reference values that could cover both the lower and higher nutrient intake levels. Inge Tetens, DK gave an overview of the terminology used in the Nordic dietary reference values which in many ways is similar to the terms adapted in other countries, regions, and international bodies – yet with important differences. The NNR do not include the term Adequate Intake (AI) but apply a Lower Intake Level (LI) that is defined differently compared with other reference values. The need for harmonization of terminologies was stressed. Anna Karin Lindroos, SE discussed the use of the LI value in the Nordic context and provided examples of assessments of inadequacy of selected micronutrient intakes using the LI cut-point and argued that the value is not needed for populations. Jan Alexander, NO, gave an overview of the Tolerable Upper intake Level (UL) that is the maximum level of total chronic daily intake of a nutrient judged to be unlikely to pose a risk of adverse health effects to humans. The UL is set to protect the population against adverse effects from high intakes of micronutrients. Examples on the derivation of ULs were provided for selenium and vitamin D through their biological adverse responses in relation to increasing intake.

As part of selected current challenges in the dual risk assessment relevant for the Nordic countries Liisa Valsta, FI presented data on the use of food supplements that has increased considerably during the past decades in all the Nordic countries. Comparisons between countries of the contribution of supplements use to the total micro-nutrient intakes revealed large differences between countries and between sexes. Lotte Høgberg, DK gave a presentation of a recent Danish vitamin D intoxication outbreak among infants. The case demonstrated an example of a national collective risk assessment action and illustrated some of legislation challenges related to food supplements compared with registered pharmaceuticals. The case also demonstrated

the need for well-established routes of communication between health authorities and the health care system.

Iodine is a nutrient that has achieved increased scientific awareness in the Nordic countries after a systematic review during the previous work for the NNR2012 revealed that the iodine status in the Nordic countries was generally not well documented. Ingibjorg Gunnarsdottir, IS and Helle Margrethe Meltzer, NO gave an overview of the Nordic situation and stressed how the Nordic co-operation had initiated new research activities with results that a least mild iodine deficiency exist in different population groups, among others pregnant women.

The lack of data for deriving dietary reference values was addressed. Hildegard Przyrembel, DE explained how extrapolation from one group to another is often applied in relation to the setting of reference values. Extrapolation can be done in relation to body mass (isometric (linear) scaling) or energy expenditure (allometric scaling). The application of both methods was discussed in relation to nutrients.

Some of the challenges in setting reference values for energy were presented by Monika Neuhaeuser-Berthold, DE. Daily energy expenditure varies relatively little within individuals, despite variation in physical activity but varies considerably among individuals even after controlling for body size. A major challenge is the setting of DRVs of energy for older adults due partly to a paucity of data regarding resting and total energy expenditure of those aged ≥ 80 years. The changes in body composition with ageing require special consideration and especially, physical activity levels of older adults likely to promote maintenance of muscle mass need to be identified.

Tommy Cederholm, SE gave an overview of the NNR2012 protein recommendation for the elderly, where disease endpoints were also considered as a criteria. He argued that a low protein intake contributes to an insufficient muscle re-modelling and muscle loss which again may lead to sarcopenia. To prevent such development, the NNR2012 increased the protein recommendation for older adults from 0.8 to 1–1.2 gram/kg body weight/day. It was stressed that a high protein intake may have negative effects on kidney function for certain groups with underlying diseases.

Elizabeth Yetley, US summarized how the committees convened by the U.S. Institute of Medicine historically have used a dual risk assessment approach to determine Dietary Reference Intakes (DRIs). A recent report recommended guiding principles for incorporating chronic disease endpoints into future DRI evaluations, with the key questions if there is a causal relationship between the nutrient and chronic disease(s), and, if so, what the nature of the quantitative intake-response curve is.

Rune Blomhoff, NO summarized his impressions of the day by expressing the appropriateness of the symposium as it addressed topics pertinent to the forthcoming update of the Nordic Nutrition Recommendations. He underlined the need for harmonization, the specific Nordic challenges, and the stimulating thoughts in relation to the approaches currently applied and the future opportunities.

In her closing remarks, Inge Tetens thanked the many excellent presentations from the invited experts and good discussions. She expressed confidence that the symposium had fulfilled its tasks – to contribute to the strengthening of the capacity of the Nordic experts involved in the forthcoming update of the NNR and to enhancing the transparency of the dual risk assessment approach in nutrition.

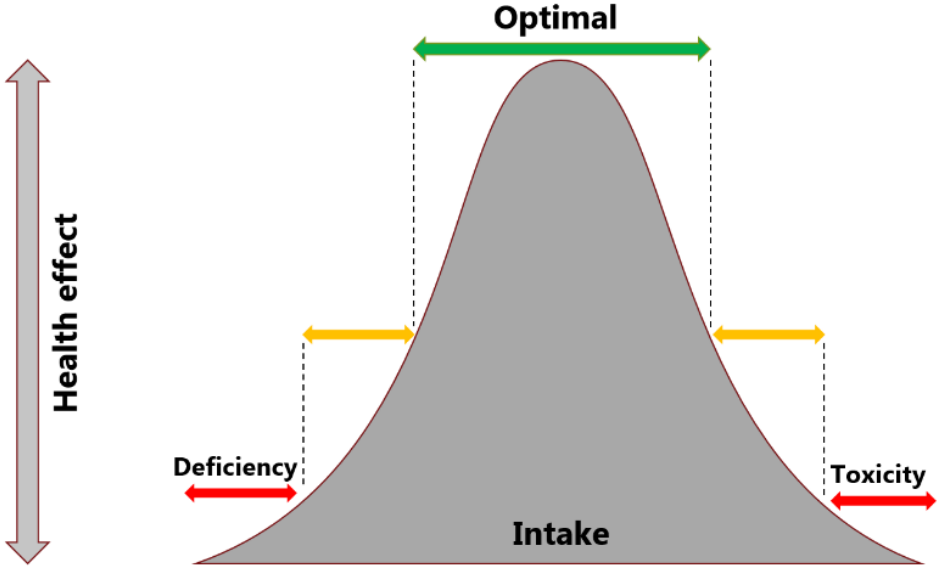
1. Background and purpose of symposium

The classical risk assessment approach offers a highly systematic framework within which information can be organized and evaluated. Contrary to non-nutrients, nutrients have a dual risk with a health risk at the low nutrient intake range (deficiency) and a risk at the high end of the nutrient intake range (toxicology).

The *purpose of the symposium* is to discuss the current use and some of the challenges in applying a nutrition risk assessment approach in setting nutrition recommendations in the light of the forthcoming update of the Nordic Nutrition Recommendations (NNR).

At the symposium *invited experts* address the methodological framework from the classical risk assessment approach as a basis for addressing the risk approach for setting nutrition recommendations and in particular for setting the criteria for the nutrient risk assessment. *Case studies* from the Nordic countries are presented to underline some of the *challenges* in applying the risk assessment approach. Especially, the *choice of criteria* and the *lack of data* for risk assessment in nutrition are addressed with examples on *extrapolations* to subgroups like children and elderly and the challenges in setting reference values for *energy and protein* with examples from *the ageing* population. Finally, the development of nutrition risk assessment using nutrient intakes and *chronic disease endpoints* is discussed.

Figure 1: The framework for the dual risk approach in nutrition



This report presents abstracts with highlights of the key points presented by the invited speakers. The discussions following the presentations are summarized in short with questions (Q), answers (A) and comments (C).

2. The Dual Risk approach in Nutrition – the concept, terminologies and approaches

2.1 Introduction to the Dual Risk concept in nutrition

Inga Thorsdottir, Professor, Dean, School of Health Sciences, University of Iceland, Iceland

Nutrition researchers have strived to define the optimal intake of nutrients for decades. The physiological roles of nutrients have served as the theoretical basis and measurements or calculations of the body's needs, usage and storage of single nutrients have been used as criteria to define the optimal intake. Recommendations for single nutrients build on defined optimal intakes with additional safety factors.

The development of the science of nutrition includes the use of a dual risk approach methodology, where both too low and too high intake levels of exposures are considered for potential adverse health effects. The focus is on the scientific evidence for various outcomes, e.g. non-communicable diseases, additionally to nutrient deficiency and toxicity, and body weight and growth.

The 5th edition of the Nordic Nutrition Recommendations (NNR2012) refers to a set of dietary reference values (DRVs) for essential nutrients and reference values for energy intake and physical activity. Food-based dietary guidelines (FBDG) are based on DRVs and evidence for health effects of food, while sustainability and environmental issues play a growing role. The 6th ed. of NNR is timely and will continue to serve as basis for health and nutrition promotion initiatives, aiming to improve public health in the Nordic countries through improvement of diet. Growth of scientific knowledge and challenges in the environment, food systems, and habits demand update of the NNR evidence. Methodological ways to work on the evidence-based recommendations are constantly improved. Further implementation of the NNR has to be strengthened.

2.2 Terminologies in nutrition risk assessment

Inge Tetens, Professor in Nutrition and Ageing, Vitality – Centre for good older lives, Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark

In the Nordic countries Dietary Reference Values (DRV) are used as the umbrella term for a complete set of nutrient references values. An overview of the terminologies used in the various versions of the Nordic Nutrition Recommendations (NNR 1 through 5) from 1980 to 2012 reflects an increased awareness that a single figure of nutrient average requirement is insufficient to cover the variety of needs for reference values that could cover both the lower and higher nutrient intake levels and that an assessment of the distribution of requirements for each nutrient would be beneficial.

In the Nordic context the term Dietary Reference Values (DRVs) denote the individual values: average requirements (AR), recommended intake (RI), upper intake level (UL), lower intake level (LI), reference values for energy intake and recommended intake range of macronutrients (Table 1).

Table 1: Terminologies used in nutrition risk assessment in the Nordic countries and other parts of the world

Nordic countries (2012)	WHO/FAO (2004)	UK (1991)	US &Canada (1994–2004)	WHO (2007)	European Commission (EFSA) (2010)
DRV *(Dietary reference values)*		DRV *(Dietary reference values)*	DRI *(Dietary reference intakes)*	NIV *(Nutrient intake values)*	DRV *(Dietary reference values)*
RI *(Recommended intake)*	RNI *(Recommended nutrient intake)*	RNI *(Reference nutrient intakes)*	RDA *(Recommended dietary allowance)*	INLx *(Individual nutrient levelx)*	PRI *(Population reference intake)*
AR *(Average requirement)*	Basal and normative nutrient requirements	EAR *(Estimated average requirement)*	EAR *(Estimated average requirement)*	ANR *(Average nutrient levelx)*	AR *(Average requirement)*
		Safe Intake	AI *(Adequate intake)*		AI *(Adequate intake)*
LI *(Lower intake level)*		LRNI *(Lower reference nutrient intake)*			LTI *(Lower threshold intake)*
UL *(Upper intake level)*	UL *(Upper tolerable nutrient intake level)*		UL *(Tolerable upper intake level)*	UNL *(Upper nutrient level)*	UL *(Tolerable upper Intake level)*
RI *(Recommended intake ranges for macronutrients)*	AMDR *(Adequate macronutrient distribution range)*	Individual minimum, maximum, and population averages	AMDR *(Adequate macronutrient distribution range)*		RI *(Recommended intake ranges for macronutrients)*

The Nordic terminology is in many ways similar to the terms adapted in other countries, regions, and international bodies. Yet, there are also important differences. Compared with other sets of reference values, the Nordic terminology does not include the term Adequate Intake (AI). AI was defined earlier by IoM and EFSA as a proxy of a recommended nutrient intake, applied when an average requirement cannot be determined due to lack of appropriate data. The AI is therefore typically applied when data from observed or experimentally determined estimates of nutrition intakes by a group of people are available.

As the use of data from observational studies and the use of biomarkers becomes more prevalent as a base for setting the DRV, careful considerations and decisions are needed as to the optimal approach for obtaining valid scientifically grounded and transparent values on the relationship between nutrient intakes and adequacy and/or health outcomes. The different terminologies used by national, regional or international agencies/bodies lead to considerable confusions, misunderstanding and even worse, misinterpretation. This has led to the common notion that harmonization of the terminologies would be warranted and various attempts have been done. Recently, a workshop held by the WHO, FAO, UNU, and the FNB of the National Academies of Sciences, Engineering, and Medicine was organized to explore the evidence for achieving global harmonization of methodological approaches to establishing nutrient recommendations.[1] Until harmonization occurs, the reference values should be interpreted and used carefully.

2.3 The approach and use of the lower intake level (LI) – can we do without it?

Anna Karin Lindroos, PhD and Senior lecturer, the National Food Agency, Uppsala and Department of internal medicine and clinical nutrition, Sahlgrenska Academy, University of Gothenburg, Sweden

The primary reference value for assessing adequacy of micronutrient intake of defined groups is average requirement (AR). Mean reported intake in a survey can be compared with AR if the intake distribution is similar to the requirement distribution. This is true for many nutrients, but not all. Values for RI, LI and UL can complement the nutrient intake assessment. This presentation will focus on LI.

Already in 1971, a three-step approach to assess dietary intake was suggested by Eeg-Larsen, Isaksson, Nikolaysen and Wretlind in the report "Veiledning til vurdering of planlegging av kosthold" published as an appendix to Näringsforskning. The lowest step, "minimum verdi", is the cut-off value below which an intake would lead to

[1] National Academies of Sciences, Engineering, and Medicine. (2018). *Global harmonization of methodological approaches to nutrient intake recommendations: Proceedings of a workshop—in brief*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24989

deficiency symptoms. This value could give an indication of risk of deficiency, but biochemical and clinical measurements have to be included in order to establish if the intake of a specific nutrient is too low or not. Based on the Eeg-Larsen report, LI was included in the first edition of the Nordic Nutrition Recommendations (NNR) and have since then been included in all the NNR editions.

However, lower intake levels are not commonly used outside the Nordic countries. In the IOM Dietary Reference Values for USA and Canada there are no values for lower intake levels and it is recommended that AR and percentiles are used in the assessment of micronutrient intake. Many countries use the IOM recommendations for assessing nutrient intake. In the UK – Lower Reference Nutrient Intake (LRNI) are used together with AR when nutrient intakes are assessed in the National Diet and Nutrition Survey. The LRNI are derived from (AR – 2 SD) and are thus not established in the same way as in the NNR, although in practice the LRNI and LI values are similar.

Examples of assessing inadequacy of selected micronutrient intakes using the NNR approach including LI cut-points and the IOM approach using the AR (or EAR) cut-point method are given, using data from Swedish women. Table 2 shows that proportions below LI did not add much additional information for vitamin D and calcium. Thus, LI values may not be needed for most micronutrients when evaluating intake in the Nordic populations.

Table 2: Distribution of selected micronutrient intakes and assessment of inadequate intake by proportions below the LI and AR cut-offs in 838 women in the Swedish National Dietary Survey 2010–2011

	Folate Intake (µg/day)	Vitamin D (µg/day)	Calcium (mg/day)
P5	129	2.23	459
P25	189	3.90	672
P50	237	5.82	849
P75	294	8.57	1,032
P95	405	14.7	1,369
AR	200 µg/day	7.5 µg/day	500 mg/day
% < AR	18 %	56 %	5 %
95 % CI	16; 20	53; 59	3.8; 6.6
% < LI	*0.1*	*6*	*2*

2.4 The approach in setting the upper level (UL) – methodologies and issues to address

Jan Alexander, Norwegian Institute of Public Health, Oslo, Norway

Like other chemical substances, vitamins and minerals (as well as other nutrients) may have adverse effects if consumed in excessive amounts (Figure 2). The purpose of setting *Tolerable upper intake levels* (UL) is to protect the population against adverse effects from high intakes of micronutrients. The UL is the maximum level of total

chronic daily intake of a nutrient judged to be unlikely to pose a risk of adverse health effects to humans.

"Tolerable intake" in this context connotes what is physiologically tolerable and is a scientific judgement as determined by assessment of the probability of an adverse effect at a given intake. The UL is not a recommended level of intake. It is an estimate of the highest level of intake, which carries no appreciable risk of adverse health effects. For nutrients, no risk of adverse effects is expected unless a threshold intake, which vary among individuals, is exceeded.

Figure 2: Responses of biological systems (beneficial responses not included)

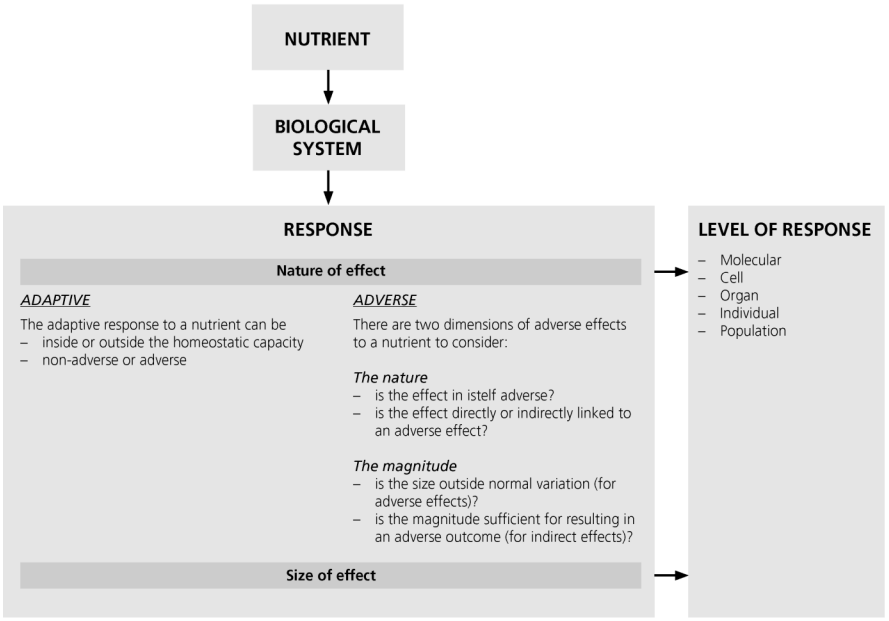
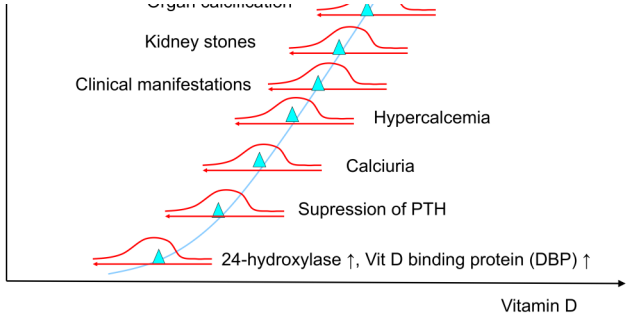
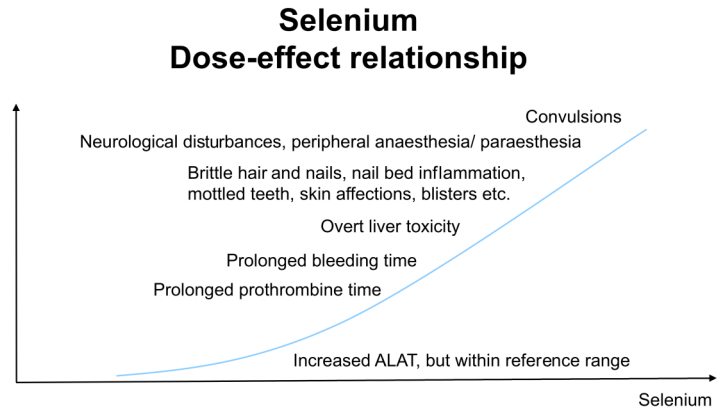


Figure 3: Dose-effect relationships for vitamin D and for selenium





Note: PTH=parathyroid hormone; ALAT=alanine amino transferase.

ULs are established close to the low end of the theoretical distribution of thresholds adverse effects. The challenge is to determine this value. Steps in the establishment of a UL include *Hazard identification* and *Hazard characterisation*. Preferably, human data, but also animal data may be used to identify evidence of adverse effects that is causally related to the exposure. Not all effects may be adverse, e.g. biomarkers, but some can be directly or indirectly linked to an adverse effect. Experimental data from animals or in vitro may be used to complement human data and provide valuable mechanistic information. The next step is *Hazard characterisation*, which includes dose-response assessment of the critical end-point and derivation of a reference point, a benchmark dose lower confidence level (BMDL) or no observed adverse level (NOAEL)/lowest observed adverse effect level (LOAEL), from which the UL is established.

Because major limitations are imprecision, lack and limited adequacy of the data on variability, uncertainty factors are used. For interspecies variation, a factor of 10 is used as a default value, but this may be lower if the data also cover the most susceptible individuals. In the absence of specific data, a default factor of 10 is used for extrapolation from animal to human data. Vitamin D and selenium will be presented as examples of the setting ULs (Figure 3).

2.5 What are the implications for NNR? Time for Q/A's

- *Q*: Do you think it is problem that we use two different levels of assessing adequate intake? We use the median intake as a reference for energy and range for macro-nutrients, but we use the average requirement for micronutrients. Does this not create a problem?
  - *A*: We use the average requirement when assessing the micronutrient intake of diets of groups of people rather than using recommended intake (RI), because the RI is meant to cover the majority of that group. If we use the RI, we will overestimate the proportion of individuals with an inadequate nutrient intake.
- *Q*: Is it true that for certain micronutrients there is no upper limit? And does this mean that these nutrients are safe to consume even in very large quantities, for instance, via highly concentrated supplements? Should we not be cautious?
  - *A*: The upper limits are based on evidence, and if the evidence is non-existing then these upper limits cannot be set. We have to advise as best as possible.
  - *A*: Yes, we should be cautious. I will give you an example of two nutrients that were first perceived to be harmless even in high concentrations. For many years it was assumed that beta-carotene and vitamin E had no upper level, but we later learned through clinical trials that both vitamins in larger doses have detrimental health effects – both increase the risk of different cancers. So, I think it is safer to assume that all micronutrients have an upper level even though we do not know this number.
- *Q*: Are the UL values based on evidence from supplements, from food or both? Does this have any implication? This seems to be confusing, because what amount can come from the diet? Do you think that the NNR should work more on including evidence from both food and supplements?
  - *A*: I think NNR should work towards including upper limits for all nutrient sources. Most of the evidence is based on supplement studies, but also on other sources and on extrapolations. For iron, for instance, the upper limit is based on supplements, so it is difficult to set the upper limit for both food and supplements (a total upper limit). Discussing upper limit for fluorine, sources such as toothpaste has also been considered.
- *Comment*: Moving forward, we should think more about the users of these reference values. I will give you two examples which are confusing to people. The

usage of average requirement, which cannot be used to assess populations, and secondly, some people are confused by the fact that Dietary Reference Values (DRVs) are sometimes given as intervals.

- *Q*: Do you know the distribution for iron requirements?
  - A: Iron requirements are not normally distributed, since the requirements are different for different age groups, particular for fertile women.
- *Q*: In Brazil we use the UL for sodium instead of the average requirement (AR), because almost all Brazilians have an intake above AR. What do you think of this method?
  - *A*: Since sodium is an essential nutrient we have both an AR and UL for sodium intake (*in the US, ed*). It is worrying that the sodium intake is at such a high level that you have to use the UL to assess the risk of excessive sodium intake in Brazil. (*In the NNR2012, the DRV for sodium is expressed as a "population goal", ed).*

3. Current Challenges in Dual Risk assessment in Nutrition

3.1 Nutrient intakes from supplements vs intakes from diets in the Nordic Countries?

Liisa Valsta, Research Manager, Adjunct Professor, Finnish National Institute for Health and Welfare (THL), Department of Public Health Solutions, Public Health Promotion Unit, Finland

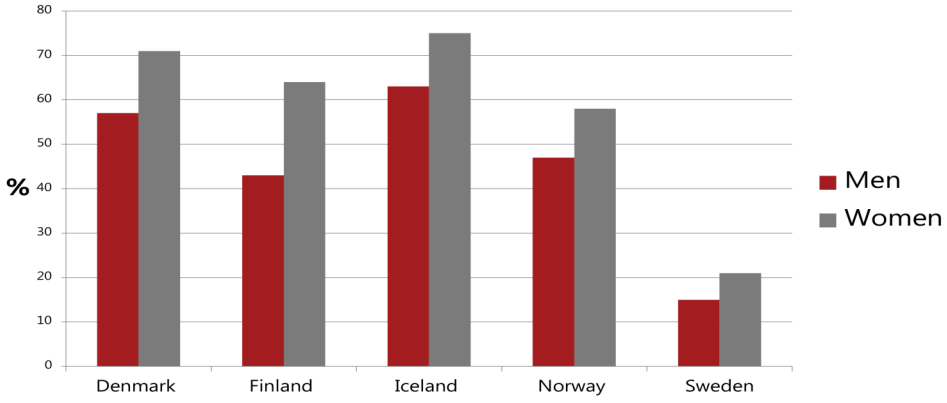
The availability and use of food supplements has increased considerably during the past decades in the Nordic Countries. The most recent supplement use and nutrient intake data are available from most of the national dietary surveys carried out in all Nordic countries between 2010–2013. Inclusion and coverage of food supplements in the national food composition databases have improved since early 1990s but varies still between countries from less than 100 supplement codes to around 1,000 codes with values available for micro-nutrient intake estimations.

In all other countries but Sweden, the prevalence of food supplement use varied in these studies around 50% among men (43–63%) and around 65% among women (58–71%). The prevalence in Sweden seemed to be lower (Figure 4). In certain population groups (e.g. among 11–50 years old Danes), the nutrient intake from food among supplement users exceeded that of nutrient intake from food of non-consumers, but not in all populations (e.g. among Finnish and Swedish adults).

Food supplements have shown to contribute to higher intakes of vitamins A, D and E, pyridoxine, iron and selenium among adolescents and young adults in Denmark. In addition to the listed nutrients, among Swedish adults also intakes of thiamine (over 3-fold), niacin, folic acid, vitamin-B12 (over 6-fold), vitamin C, calcium, magnesium, zinc have shown to be higher among supplement users compared to non-users. Similar pattern is seen also in Finland with over 2-fold intakes of thiamine, riboflavin, pyridoxine, vitamin B12 among both men and women using supplements and among men also in intakes of Vitamin C and magnesium compared to non-users. In Iceland, the additional micro-nutrient intake as % from food supplements compared to the intake from foods varies between 10–70%. The largest contributions (>40%) are seen in intakes of vitamin E, vitamin B6, vitamin C and molybdenum. In Norway, intakes of vitamins D, E and C are higher among men and women using supplements and vitamin C and iron intakes among women using supplements, but the increases in intakes have been moderate. Retinol, iron, zinc intakes among Danish children, pyridoxine, zinc and calcium intakes among Finnish adults and pyridoxine, folic acid, vitamin C and iron have

shown to exceed the Tolerable Upper Intake Limit (UL) due to supplement use, but usually only in a small proportion of the population.

Figure 4: Proportion of adults in the Nordic countries using food supplements



Sources: DANSA 2010-13, FINDIET 2012, National Icelandic Dietary Survey 2010-2011, Norkost 3, 2011, Riksmaten 2010-2011 (partly unpublished data)
Supplement composition databases since 1990s – from <100 items to around 1000 items

Source: DANSA 2010–13, FINDIET 2012, National Icelandic Dietary Survey 2010–2011, Norkost 3, 2011, Riksmaten 2010–2011 (partly unpublished data).

Comparison of contributions of supplement use to micro-nutrient intakes between countries include uncertainties due to differences in data collection methods, reference period and frequency of supplement use in focus.

3.2 Infants and vitamin D intoxication, recent outbreak in DK

Lotte CG Hoegberg, on behalf of the National Vitamin D outbreak Workgroup

The National Vitamin D outbreak Workgroup are: Søren Bøgevig (1), Lotte Hoegberg Cg (2), Anders Schou J (3), Ida Schmidt M. (4), Fie Vojdeman J. (5), Konstantinos Kamperis (6), Christian Mølgaard (7), Christine Brot (8), Henrik Christesen (3).

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Subtitle: National vitamin D intoxication outbreak among infants due to a manufacturing error of vitamin D droplets: Challenges for the health care system.

Objective: Danish Health Authorities (DHA) recommend vitamin D supplementation for children up to two years with 10 micrograms (400 IU)/day, equal to five droplets of 2 microgram/droplet. An erroneous manufactured vitamin D product was identified in July 2016 after an infant had developed severe vitamin D intoxication, despite a daily dose of the recommended five drops. We describe the first 10 days of the outbreak and identify risk assessment and risk communication between involved physicians from The Danish Poisons Information Centre (DPIC), The Danish Paediatric Society (DPS) and DHA.

Case Series: Laboratory analysis performed by the Danish Veterinary and Food Administration showed that the specific vitamin D product contained 150 microgram/droplet instead of the intended 2 microgram/droplet. Infants dosed as recommended therefore received 750 micrograms (30,000 IU) daily. There was no concentration stated on the label. The manufacturing company acclaimed the production of 500 bottles (each 10 ml) due to a human error in the manufacturing process. The product was immediately withdrawn. A total of 340 bottles were already sold from March 2016.

Nine days after withdrawal of the product the DHA had identified 150 children <2 years at risk of intoxication. Of those 87 children had already been diagnosed with s-25-hydroxy vitamin D >150 nmol/L. Serum ionized calcium >1.35 mmol/L was detected in 76 infants, and 18 infants had severe hypercalcemia with ionized calcium of >1.49 mmol/L. Symptoms included reduced appetite, vomiting, irritability and failure to thrive. A few patients had severe symptoms. We developed an urgent national tracing, diagnosis and treatment algorithm for vitamin D intoxication. Warnings and public emergency announcements were issued from the DHA and a strategy for keeping the media attention to the matter was made between DPIC, DPS and DHA to ensure identification and management of all exposed infants.

Conclusion: The outbreak occurred in the summer holiday and our collective risk assessment drew attention to the importance of thorough medical examination of all exposed patients, preferably in a hospital setting. Errors in distribution of important information regarding triage and treatment according to new guidelines within the healthcare system were seen in numerous situations in the first days. This case series illustrate the legislation challenges by categorization of potentially toxic substances as food supplements instead of registered pharmaceuticals and the need for well-established routes of communication between health authorities and the health care system.

3.3 Pregnancy/lactation and iodine, recent situation in Nordic countries

Ingibjörg Gunnarsdóttir, Unit for Nutrition Research, Faculty of Food Science and Nutrition, University of Iceland & Landspitali National University Hospital, Island

Presented by Helle Margrete Meltzer, Research director, Management and Staff for Infection Control and Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

A number of systematic literature reviews formed the basis for establishment of dietary reference values in the 5th edition of Nordic Nutrition Recommendations (NNR) 2012. In one of them, recent scientific data on health effects of iodine status (as an indicator of iodine intake) was reviewed. Pregnancy is one of the most critical periods for iodine deficiency where inadequate maternal iodine status might have adverse effects on fetal neurodevelopment.

One of the main results of the systematic review *Iodine intake in human nutrition* for the 5th edition of the NNR was that the iodine status in the Nordic countries was in general not well documented. At the time, the majority of studies in the area of iodine nutrition from the Nordic countries were from Denmark. Following discussions on the situation at the 10th Nordic Nutrition Conference in Reykjavik 2012 were the 5th edition of the NNR were presented, a small group of scientists gathered to establish a Nordic collaboration aiming at encouraging studies in this field. The first Nordic Iodine meeting took place in Gothenburg in October 2013, followed by meetings in Copenhagen 2014, Bergen in 2015 and Reykjavik 2017.

Since 2012 the number of publications in the area of iodine nutrition from the Nordic countries has increased considerably, and we now have data suggesting at least mild iodine deficiency in many different population groups in the Nordic countries, including pregnant women.

Below is a selection of Nordic articles published since 2012.

Box 1: List of references from Nordic countries on iodine nutrition

I. Gunnarsdottir I, Gustavsdottir AG, Steingrimsdottir L, Maage A, Johannesson AJ, Thorsdottir I. Iodine status of pregnant women in a population changing from high to lower fish and milk consumption. Public Health Nutr. 2013 Feb;16(2):325-9. https://www.ncbi.nlm.nih.gov/pubmed/22607718

II. Brantsæter AL, Abel MH, Haugen M, Meltzer HM. Risk of suboptimal iodine intake in pregnant Norwegian women. Nutrients. 2013 Feb 6;5(2):424-40. https://www.ncbi.nlm.nih.gov/pubmed/23389302

III. Granfors M, Andersson M, Stinca S, Åkerud H, Skalkidou A, Poromaa IS, Wikström AK, Nyström HF. Iodine deficiency in a study population of pregnant women in Sweden. Acta Obstet Gynecol Scand. 2015 Nov;94(11):1168-74. https://www.ncbi.nlm.nih.gov/pubmed/26292156

IV. Kirkegaard-Klitbo DM, Perslev K, Andersen SL, Perrild H, Knudsen N, Weber T, Rasmussen LB, Laurberg P. Iodine deficiency in pregnancy is prevalent in vulnerable groups in Denmark. Dan Med J. 2016 Nov;63(11). https://www.ncbi.nlm.nih.gov/pubmed/27808034

V. Henjum S, Lilleengen AM, Aakre I, Dudareva A, Gjengedal ELF, Meltzer HM, Brantsæter AL. Suboptimal Iodine Concentration in Breastmilk and Inadequate Iodine Intake among Lactating Women in Norway. Nutrients. 2017 Jun 22;9(7). https://www.ncbi.nlm.nih.gov/pubmed/28640217

VI. Abel MH, Caspersen IH, Meltzer HM, Haugen M, Brandlistuen RE, Aase H, Alexander J, Torheim LE, Brantsæter AL. Suboptimal Maternal Iodine Intake Is Associated with Impaired Child Neurodevelopment at 3 Years of Age in the Norwegian Mother and Child Cohort Study. J Nutr. 2017 Jul;147(7):1314-1324. https://www.ncbi.nlm.nih.gov/pubmed/28515161

VII. Abel MH, Ystrom E, Caspersen IH, Meltzer HM, Aase H, Torheim LE, Askeland RB, Reichborn-Kjennerud T, Brantsæter AL. Maternal Iodine Intake and Offspring Attention-Deficit/Hyperactivity Disorder: Results from a Large Prospective Cohort Study. Nutrients. 2017 Nov 13;9(11). https://www.ncbi.nlm.nih.gov/pubmed/29137191

VIII. Brantsæter AL, Knutsen HK, Johansen NC, Nyheim KA, Erlund I, Meltzer HM, Henjum S. Inadequate Iodine Intake in Population Groups Defined by Age, Life Stage and Vegetarian Dietary Practice in a Norwegian Convenience Sample. Nutrients. 2018 Feb 17;10(2). https://www.ncbi.nlm.nih.gov/pubmed/29462974

IX. Henjum S, Aakre I, Lilleengen AM, Garnweidner-Holme L, Borthne S, Pajalic Z, Blix E, Gjengedal ELF, Brantsæter AL. Suboptimal Iodine Status among Pregnant Women in the Oslo Area, Norway. Nutrients. 2018 Feb 28;10(3). https://www.ncbi.nlm.nih.gov/pubmed/29495606

3.4 What are the implications for NNR? Time for Q/A's

3.4.1 Q/A's re nutrient intakes from supplements

- *Q*: It must be complicated to assess the nutrient intake from foods, fortified foods and dietary supplements? How is this done?
  - *A*: We take into account intakes from both foods, fortified foods and supplements. But it would be interesting to see the whole picture and be able to take into account the bioavailability of nutrients, which could be different in fortified foods compared and non-fortified foods. Also, it would be interesting to compare the fortification practices in different countries.
- *Q*: Can you comment on the high vitamin D intake in Finland?
  - *A*: We fortify a range of different food products with vitamin D in Finland, for instance, both skim and fatty milk, yoghurt and spreads. So, these fortified food products are probably explaining the high vitamin D intake in Finland.

3.4.2 Q/A re vitamin D intoxication

- *Q*: How did this product (*vitamin D supplement, ed.*) end up on the market – is there no control of food supplements in Denmark?
  - *A*: Anyone can produce supplements in Denmark and this production is not subjected to the same strict production criteria, as is the case for medical products. For instance, they only need to test the concentration in relatively few random samples, not in every batch produced. We should perhaps reconsider this practice to avoid these types of accidents. This product was not sold in a pharmacy, which typically has a strict product control. It was only sold in physical or online health food stores.
- *Q*: So the manufacture is not liable?
  - *A*: Yes, certainly they are.
- *Q*: Did this case make international news because other countries could learn from this incidence. Informing other countries could be important since this learning about this event could perhaps prevent it from happening in other places.
  - A: Yes, it made both European and North American news, so a lot of international attention was brought on by this incident.
- *C*: There are few cases in the history concerning vitamin D intoxication, but yours seem to be unique since the exposure were vitamin D alone, not in a combination with other nutrients.
  - *A*: Yes, but we have done a literature search regarding relevant studies and will compare these data to our own. A scientific article will be published sometime in the future.

3.4.3 Q/A re iodine during pregnancy/lactation

- *Q*: In case of the "correlation between low iodine and ADHD/low IQ" – is there any causal evidence of the relationship?
  - *A*: This is based on observational studies. We have of course corrected for potential confounders, but we never know for sure with this type of evidence. However, there is a British study (ALSPAC study) indicating the same – low iodine concentration in pregnant women and low IQ score in their offspring, and more studies are coming from Norway that are showing similar results.
- *Q*: Is it correct that there is no fortification of salt with iodine in Norway and Iceland, while this is the practice in Finland, Denmark and Sweden?
  - *A*: We have very different practices in the Nordic countries when it comes to fortification of foods. For instance, Norway has 10 times less iodine in their salt compared to Sweden – 5 µg vs. 50 µg per gram of salt. Iceland (*like Denmark, Norway and Sweden, ed*) has both fortified and non-fortified salt. In Finland they have 25 µg per 1 gram of salt. So, despite the similarities between our countries, there are large differences in how we fortify our salt.

In Norway the National Nutrition Council has recommended the Norwegian government to do something about the low iodine intake in Norway, but we also have to consider the potential negative consequences of such actions. For instance, many two-year olds already have an intake above what is recommended in Norway due to high milk consumption. Fortification is therefore a balance. We have to make sure that we are not increasing the number of children that are reaching the UL for iodine due to fortification. In general, we have to be cautious because there is a relatively narrow gap between recommended intake and the UL for iodine.

- *Q*: Should we not focus more on recommending iodine for pregnant women when we know they are likely to be a high-risk group?
  - *A*: We do not have data for all of the population and some of the data we have indicate that iodine supplementation in pregnant women has no effect. Increasing iodine intake in pregnant women with low iodine concentrations can shock the "thyroid system" and even have the opposite effect. So we have to be careful in regards to recommending iodine intake in pregnant women even though they might have a low iodine intake.

4. Filling the Data Gaps – extrapolations

4.1 Extrapolations – allometric or isometric scaling?

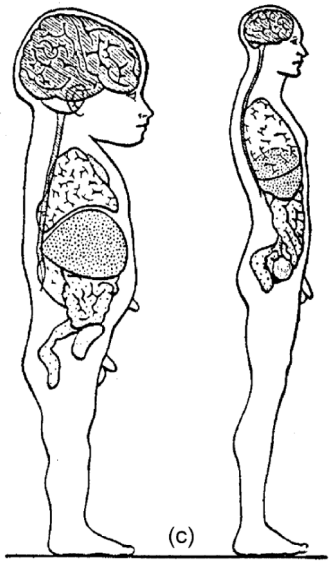
Hildegard Przyrembel, Germany

Dietary reference values (DRVs) are often set based on data from particular population groups characterised according to age, sex and possibly also environmental conditions. For population groups for which data are lacking or which differ in characteristics extrapolation is needed to arrive at DRVs (rarely interpolation between two adjacent population groups).

Extrapolation can be done in relation to body mass or, less often, in relation to energy expenditure (expressed as nutrient density, e.g. niacin). Not all nutrients are equal! There are those whose requirement is apparently proportionate to total body mass (e.g. potassium as considered by EFSA) and there are those whose requirement is not proportionate to total body mass but assumed to be proportionate to the sum of masses of metabolically most active organs/tissues.

In the first instance we speak of isometric (linear) scaling, in the second of allometric scaling, using body mass with an exponent, mostly of 0.75 (e.g. most vitamins of the B group). Because the relationship of metabolically most active organs/tissues (liver, brain, kidney, intestine) to total body mass changes during growth and development (as does also the relationship of metabolically less active organs/tissues, such as muscle, adipose tissue) presumably the appropriate exponent to body mass changes too (Figure 5).

Figure 5: Differences in body proportions between a new-born and an adult



Source: Adapted from Valentin, J. (ed.). *Annals of the ICRP: Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values*. Published for The International Commission on Radiological Protection by PERGAMON, 2003. Elsevier Science Ltd., fig. 4.9, p.82: "Right lateral views of the newborn infant and adult male reconstructed to the same height (Scammon, 1953). (a) The skeleton, (b) the musculature, subcutaneous tissue, and skin, and (c) the major visceral mass and the central nervous system." Only panel c is presented here. Licensed under Creative Commons Attribution-Sharealike 3.0 Unported and GNU Free Document.

The fact is, that we know little about the correctness of these assumptions: 1) the appropriate exponent for body mass and 2) which nutrients require allometric scaling and how can we prove it. For demonstration of this uncertainty, the scaling procedures performed by the USA FNB and by EFSA are shown in comparison.

Table 3: Comparison of the scaling approach used by the FNB of the IoM and EFSA (different approaches in italics)

	FNB	EFSA
Isometric scaling Minerals	Calcium, fluoride, magnesium, manganese	Calcium, fluoride, *iodine*, magnesium, manganese, *molybdenum*, potassium, *selenium*
Isometric scaling Vitamins		Niacin, *thiamin*, vitamin C, vitamin E
Allometric scaling Minerals	Chronium, copper, *iodine*, *molybdenum*, *selenium*, zinc	Copper
Allometric scaling Vitamins	Biotin, *thiamin*, choline, niacin, vitamins B2, B6, B12, A, C, E, K, folate, pantothenic acid	Biotin, vitamins A, B2, B6, B12, C, E, K, folate, pantothenic acid, choline, folate

4.2 Challenges in setting reference values for energy

Monika Neuhäuser-Berthold, Institute of Nutritional Science, Justus Liebig University, Giessen, Germany

Dietary reference values (DRVs) of energy for adults aim to maintain a body mass that has been associated with lowest morbidity and mortality. Such values are based on measurements of either total energy expenditure using the doubly labelled water method or of the various components of energy expenditure using indirect calorimetry and the factorial approach in reference populations. Both techniques have specific advantages and disadvantages.

Although it is recognized that, beside body mass body composition is the major determinant of energy expenditure, the extent to which variation in the energy expenditure of individual tissues and organs can explain the diversity in energy expenditure among individuals needs to be further explored. It has been observed that daily energy expenditure varies relatively little within individuals, despite variation in physical activity and that it varies considerably among individuals even after controlling for the effect of body size. This suggests that energy expenditure is controlled at an individual set-point for energy expenditure. In how far genetics and metabolic processes such as adaptive thermogenesis may be involved in the regulation of energy expenditure awaits further elucidation.

A major challenge is the setting of DRVs of energy for older adults who are considered as the fastest growing segment of the population. There is a paucity of data regarding resting and total energy expenditure of those aged ≥ 80 years. Aging is generally associated with an increase in body mass until an age up to about 70 years, when it begins to decline. There is also a progressive decline in energy intake and daily total energy expenditure. Characteristic changes in body composition during the course of aging are an increase in fat mass with a greater proportion of abdominal and visceral fat while muscle mass decreases. These changes require special consideration in the derivation of DRVs of energy for this age group and especially, physical activity levels of older adults likely to promote maintenance of muscle mass need to be identified.

Table 4: DRVs and energy intake for the ageing population

DRVs and energy intake for the ageing population
There is uncertainty about the target BMI in older adults Several studies have reported an attenuation of the U- or J-shaped BMI mortality curves Some studies have reported a minimum mortality at higher BMI in older subjects than younger subjects Recent Opinions on DRVs of energy from EFSA (2013) and D-A-CH (2015) did not include specific BMI ranges for older because of the evidence for this was considered insufficient

Facing the increasing prevalence of overweight and obesity, the role of energy expenditure, with regard to energy imbalances cannot be regarded independently from energy intake. Methods allowing accurate energy balance studies may contribute to a better understanding of the underlying mechanisms that lead to changes in body mass and body composition in individuals.

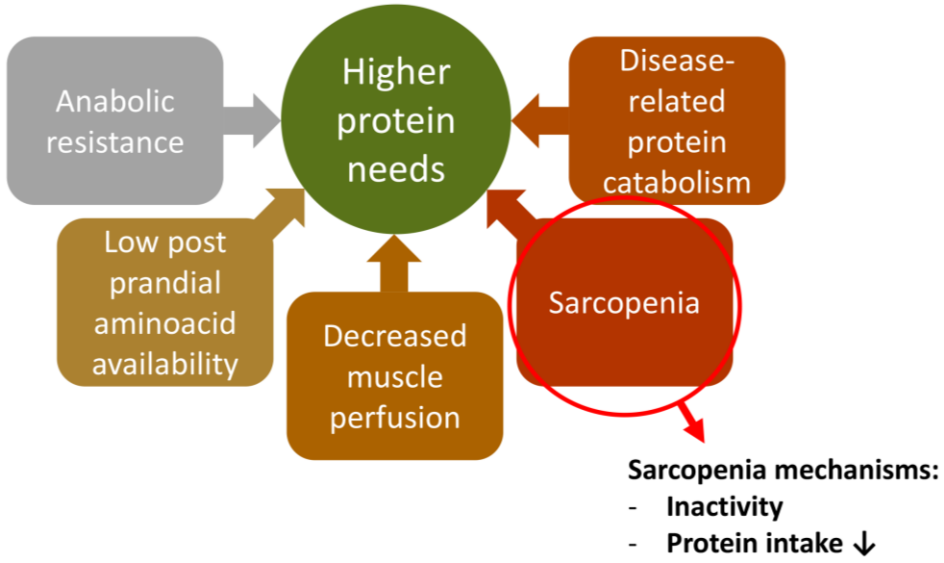
4.3 Elderly and protein recommendation – when disease endpoints are also considered

Tommy Cederholm, MD, PhD, Professor, Clinical Nutrition and Metabolism, Uppsala University, Theme Ageing, Karolinska University Hospital, Sweden

Protein is a nutrient with the potential to impose health risks when intake is high as well as low. Furthermore, a reduced protein intake may be linked both to detrimental as well as under some conditions beneficial effects.

In older people a low protein intake contributes to an insufficient muscle re-modeling and muscle loss. When muscle mass reduction passes a certain degree muscle function is at stake, leading to sarcopenia. In general, people tend to reduce their protein intake with increasing age. Protein deficiency is one possible reason for sarcopenia, which contributes to the development of frailty, a less independent life-style and eventually to disability. In order to prevent such development, the previous NNR2012 increased the protein recommendation for older adults from 0.8 to 1–1.2 gram/kg body weight/day.

Figure 6: Reasons for increased protein needs in the elderly. NNR 2012 recommends range in E%, target and corresponding g/kg bw



A high protein intake may have negative effects on kidney function, based on the observation that a high intake induces glomerular hyper-filtration with local glomerular hypertension, leading to glomerular damage. Chronic kidney disease (CKD) is usually the result of an underlying disease like diabetes, hypertension or glomerulonephritis. There is no evidence that protein *per se* could cause CKD. However, in patients with CKD a reduction to 0.6–0.8 gram protein/kg body weight/day may reduce glomerular stress, slow down the pace of kidney damage, and may postpone dialysis.

Protein sources are many; i.e. red meat from beef and game, white meat from poultry, fish, dairy products and vegetables, e.g. legumes, nuts, bread etc. Recent evidence indicates that it's mainly the intake of red meat that has negative effects on glomerular filtration rate (GFR), whereas a plant-based diet with even high intake of white meat and plant-derived proteins may be beneficial for kidney function. On the other hand, animal protein has a higher quality, i.e. a more muscle beneficial amino acid composition.

It appears that for older people without CKD the risk of malnutrition and sarcopenia due to a too low protein intake is higher than the risk of CKD development due to high protein intake. Thus, for healthy older adults, protein recommendation could be maintained at 1–1.2 g/kg body weight/day. In older people with CKD (GFR <60 ml/min/1.73m^2) it could still be advisable to reduce protein intake to <0.8 g/kg body weight/day.

4.4 What are the implications for NNR? Time for Q/A's

4.4.1 Q/A's re extrapolation

- *Q*: Do we know that the requirement for all nutrients is related to energy expenditure? This might not be true for all nutrients.
  - *A*: You are exactly right. We cannot prove this is the case. We have energy expenditure per organ in relation to total body weight, but we do not know whether nutrient requirements change proportionally to changes in energy expenditure. We simply do not have the data, unfortunately. One way to examine this, would be look at the activity of vitamin-depending enzymes in different organs and see how these change, but such data are also not available.

4.4.2 Q/A's re reference values for energy

- *Q*: Sometimes you meet elderly people who eat relatively little food, but are not losing weight. What is the explanation for this you think? Are these elderly in a kind of starvation mode?
  - *A*: First of all, to make a correct judgement I would have to examine the foods being consumed in the specific case and also examine the energy

expenditure. However, it is likely explained by the decrease in energy expenditure seen in elderly people. They therefore need less energy to maintain their body mass. There is a kind of adaptation occurring, where a new set point for the energy expenditure relative to the body mass is set.

- *Q*: You mentioned that some foods might enable a change of white fat to brown fat that could thereby increase energy expenditure. Can you elaborate a bit in regards to this topic?
  - *A*: Some studies have shown that certain amounts and certain food ingredients can affect the sympathetic nervous system and lead to white fat being turned into beige or brown fat. This is a fascinating research topic, but there is still much to be learned.
- *Q*: You mentioned that EFSA and also the NNR set an optimal BMI of 22.5 and 23 kg/m^2, respectively. But in regards to the elderly this is challenging. Do we know whether this is an optimal BMI also for the elderly?
  - *A*: Correct, the given BMI values for the elderly might not be optimal since we have very little data on older people, especially people that are 80+ years of age. We have used the BMI for younger people, but this is likely not optimal. Also, the concept of BMI does not take into account the body composition, which is also a very important aspect.

4.4.3 Q/A's re elderly and protein recommendations

- *Q*: What about recent evidence suggesting that increased protein intake can lower insulin sensitivity?
  - *A*: I am not too familiar with these studies, but one of the reasons why elderly should consume adequate protein is to maintain muscle mass, which is also important for insulin sensitivity. The increased fat mass and decrease in muscle mass can likely increase the risk of insulin resistance. We do not propose high amounts of protein, we propose relatively minor increases in protein intake and we think that the benefits outweigh the potential negatives.
  - *A*: It could also be that it is the low intake of carbohydrates that is affecting insulin sensitivity and not the protein. It is difficult to figure out whether it is one or the other.
- *Q*: Which clinical measurements did you primarily rely on when giving these (*higher, ed*) protein recommendations for the elderly?
  - *A*: It was perhaps more a question of the protein intake needed for a lowering of the risk factors. We have a number of different studies conducted in different settings showing that elderly people lose muscle mass at a lower protein intake. We also have studies showing that higher protein intake is beneficial for both muscle mass as well as muscle function.
- *Q*: So muscle function is a good outcome to use when it comes to the elderly?

  - *A*: Yes, definitely. The most important outcome in elderly is muscle function.
- *Q*: Did you also use N-balancing studies where physical activity was taken into account?
  - *A*: I have no experience with performing N-balancing studies myself. I do not think that too many of such studies are done nowadays. To my knowledge, there are no N-balancing studies looking at physical exercise. They are all related to N-equilibrium.
- *Q*: So did you measure muscle size and function in your studies?
  - *A*: Yes, we did both. Most importance was given to muscle function.
- *Q*: It seems to me that some of the evidence was based on studies where protein was not the only exposure. For instance, some of the studies also included intake of vitamin D in addition to the protein. How did you determine whether it was actually the protein that had an effect on muscle size and function?
  - *A*: Of course, in such studies it is difficult to tell what is affecting the outcome, but not all studies were using mixed exposures. Some of the strongest evidence comes from observational studies where this should not be a large problem. But here we of course need to recognize the limitations of measuring food intake via FFQs. In addition to the observational data, we also have a number of short-term experimental studies showing a positive effect of both protein- and amino acid intake on protein synthesis. We know that one of the stronger anabolic stimuli of protein synthesis is protein intake, but it is also possible that some adaptation will occur after some days, so we cannot rely on short term studies only.
- *Q*: Did you include any studies from the Nordic countries in your systematic reviews? It looks as though a lot of the evidence comes from the U.S., but dietary patterns might be quite different here in the Nordic countries? It might be that it is the complete diet and not only the protein intake that influences muscle mass and function in the elderly.
  - *A*: There were not too many studies from the Nordic countries. Most are from the U.S, and yes, dietary patterns are different. These are of course weaknesses that one needs to consider when interpreting the results.
- *Q*: What about the frequency of protein intake, is that not important?
  - *A*: We do not know for sure. There are some controversies regarding this research question. There are some indications that you need 20–25 perhaps even 30 grams of protein per meal for an optimal stimulation of the protein synthesis. To be "safe", you could space out your protein intake at the different meals and try to consume around 25–30 grams or so per meal.

5. Where do we go from here?

5.1 Options for Basing Dual Risk Assessment on Chronic Disease Endpoints

Elizabeth A. Yetley, Ph.D. Retired, Sr. Nutrition Research Scientist, U.S. National Institutes of Health

Historically, committees convened by the U.S. Institute of Medicine have used a dual risk assessment approach to determine Dietary Reference Intakes (DRIs) for both prevention of deficiencies and for definition of tolerable upper intake levels. These committees also prioritized the use of chronic disease endpoints for deriving DRIs.

However, only 4 nutrients had sufficient evidence for considering chronic disease endpoints: saturated fat, trans fat, sodium, and fluoride. For trans and saturated fats, the threshold intake assumptions of the dual risk approach were not met and no DRI was provided. For sodium, an Adequate Intake (AI) reference value was based on practical considerations, not the dual risk model. A recent report recommended guiding principles for incorporating chronic disease endpoints into future DRI evaluations[2].

These principles address two questions: 1) is there a causal relationship between the nutrient and chronic disease(s), and, if so, 2) what is the nature of the quantitative intake-response curve? The first question has not been needed for reference values for prevention of nutrient deficiencies because their essentiality is generally considered "settled science". A major challenge in evaluating causality for chronic disease endpoints is that the strongest evidence is generally derived from randomized controlled trials (RCTs), but there are limited numbers of RCTs for nutrition and chronic disease relationships. Surrogate disease markers in place of chronic disease outcomes lend themselves to RCT designs, but the process of "qualifying" surrogate markers has had only limited success with nutrients.

[2] The National Academies of Sciences, Engineering, Medicine. 2017. Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease. The National Academies Press. Washington, DC

Box 2: Description of surrogate markers

Surrogate marker:

- Intended to substitute for a clinical endpoint;
- Expected to accurately predict clinical benefit or harm.

Surrogate markers provide scientific and economic efficiencies:

- Shorter duration;
- Smaller sample sizes;
- Lower costs.

If a causal relationship is found between a nutrient intake and a chronic disease risk, the second question is how best to quantify an intake-response curve? Evidence to support this question is often derived from observational studies. One challenge is that, unlike the linear intake-response curves observed for nutrient deficiencies and traditional upper intake levels, intake-response curves for nutrients and chronic diseases are often non-linear in nature.

Moreover, they rarely exhibit the threshold effect seen with classical nutrient deficiencies. For this reason, the recent "Guiding Principles" report from the NAS recommends that intake reference values for chronic disease endpoints be based on intake ranges rather than on single point values.

Box 3: List of publications on chronic disease endpoints

I. Institute of Medicine. 2006. Dietary Reference Intakes. The Essential Guide to Nutrient Requirements. The National Academies Press. Washington, DC. https://www.nal.usda.gov/sites/default/files/fnic_uploads/DRIEssentialGuideNutReq.pdf

II. Institute of Medicine. 2010. Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease. The National Academies Press. Washington, DC. https://www.ncbi.nlm.nih.gov/books/NBK220297/

III.The National Academies of Sciences, Engineering, Medicine. 2017. Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease. The National Academies Press. Washington, DC. http://www.nationalacademies.org/hmd/Reports/2017/guiding-principles-for-developing-dietary-reference-intakes-based-on-chronic-disease.aspx

IV. Yetley EA, MacFarlane AJ, Greene-Finestone LS, Garza C, Ard JD, Atkinson SA, Bier DM, Carriquiry AL, Harlan WR, Hattis D, King JC, Krewski D, O'Connor DL, Prentice, RL, Rodricks JV, Wells GA. 2017. Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group. Am J Clin Nutr 105(Suppl):249S-85S. https://academic.oup.com/ajcn/article/105/1/249S/4569850

V. Yetley EA, DeMets DL, Harlan WR Jr. 2017. Surrogate disease markers as substitutes for chronic disease outcomes in studies of diet and chronic disease relations. Am J Clin Nutr 106(5):1175-1189. https://academic.oup.com/ajcn/article/106/5/1175/4822346

5.2 What are the implications for NNR? Time for Q/A's

- *C*: I would recommend that you also include relevant studies that make use of Mendelian randomization. These studies can contribute important information when trying to establish causal pathways between lipoproteins and cardiovascular endpoints. This is also true for the so-called "natural studies" where certain areas such as a specific country or municipality enforce a legislative restriction on trans-fatty acids and where comparisons then can be drawn from changes in cardiovascular disease outcomes. This has been done in, for instance, Denmark and in the state of New York.
  - *A*: Yes, such studies were recognized, but it did not change our overall assessment of the evidence between lipoproteins and cardiovascular disease. We acknowledge that surrogate measures can be complex. There can be multiple pathways. So there is still much to learn.
- *Q*: Since chronic diseases are multifactorial I am surprised that you use a single surrogate marker for assessing cardiovascular risk. You could use complex surrogate markers instead where you take into account additional factors such as inflammatory markers.
  - *A*: The more parameters you can measure the surer you are of course. It is recommendable to measure multiple markers to better assess the risk. This will give you a more confident correlation. However, in order to use complex surrogate measures, we need to be able to explain multiple pathways. Often though, we still need a lot of knowledge on these pathways.
- *C*: I think that more studies need to take into account the baseline status of the investigated nutrients. This is not done often enough. You supplement these groups without knowing their baseline levels. No surprise that some studies therefore show different results.
  - *A*: Yes, accounting for nutrient status at baseline can be important.
- *C*: We probably have to carefully define the target population when looking at surrogate markers. For instance, unmeasured baseline values can determine whether or not you find an effect of the intervention. If these baseline values are unaccounted for, it might be a problem.
  - *A*: Yes, one of the important things is how you define your study population. For example, if you only include healthy people in your study population, you have excluded half of the population. Therefore, you need to be very clear about the reasons for choosing your population and why the chosen population is a good fit for your study. Also, you need to be very clear about for whom the results are relevant.
- *Q*: Is it possible to assess chronic disease markers in children?
  - *A*: With chronic disease markers you want to be careful in extrapolating between different populations and we are missing a lot of data, for instance,

in regards to children, obese people, people with hypercholesterolemia and other subgroups of the population.

- *Q*: You said that the concept of reference intervals could be difficult to interpret for some users. Can you elaborate?
  - *A*: Yes, as a user, reference values can be difficult to interpret when they are given as ranges. You have to consider this issue from a user perspective. Furthermore, when providing reference values in the form of a range, the food industry will tend to use the highest intake value and health professionals will use the lower intake value.
- *Q*: Since a large part of the population is now obese should we concentrate on making specific nutritional recommendations for obese individuals as their requirements might be different, or should we concentrate on trying to prevent people from becoming obese?
  - *A*: Prevention has so far not been successful and we are faced with a double burden where a lot of overweight individuals also are deficient in several nutrients. The majority of our population is now overweight, so we have to consider this issue.
- *Q*: In relation to nutritional recommendations, should we be considering the food matrix and the bioavailability of different nutrients when we are setting the reference values?
  - *A*: Yes, even though this can be complex, we should try to include these aspects also. This has to some extend also been considered in our current nutritional guidelines.

5.3 Impressions of the day

Rune Blomhoff, Professor, Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Norway and project leader of a proposal for the 6th Edition of Nordic Nutrition Recommendations NNR2022

Rune Blomhoff expressed the appropriateness of the symposium as it addressed several topics pertinent to a forthcoming update of the Nordic Nutrition Recommendations.

Rune Blomhoff's impression was that the terminologies in relation to dietary reference values was a specific challenge and reminded the audience that an international attempt for a global harmonization of methodological approaches to nutrient intake recommendations was currently undertaken by US FNB, WHO and FAO. The Nordic NNR work should follow this development closely.

The workshop had contributed considerably to the scientific considerations in relation to dietary reference values by underlining the complexity of setting of the values and the needs and importance of cross-disciplinary collaboration. An important

lesson from the day was also the need to continuously address the specific Nordic challenges in relation to certain Nordic practices and specific nutrients.

The presentations and discussions of the data – or rather the lack of data – and the various approaches to deal with the lack had been interesting and stimulated further thoughts. The needs for specific data for certain groups of the population, including the elderly had become very clear. Also, the presentation and the discussion in relation to markers of chronic diseases had been inspiring and useful for the future Nordic work on the common Nordic Nutrition Recommendations.

5.4 Closing remarks

Inge Tetens, Professor in Nutrition and Ageing, VITALITY – Centre for good older lives, Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark

In her closing remarks, Inge Tetens expressed special thanks to the many excellent presentations from the invited experts and good discussions with participants during the day. She expressed confidence that the tasks of the symposium – to strengthen the capacity of the Nordic experts involved in the forthcoming review and update of the Nordic Nutrition Recommendations and to enhance the transparency of the dual risk assessment approach and methods applied – had been fully achieved. And it was her hope that the report to be published from the day would have a further reach to other nutrition colleagues and stakeholders.

Finally, Inge Tetens thanked the Project group for excellent team work in the preparation of the symposium, the NKMT for its instrumental role in financing the symposium, and expressed appreciation to "Vitality – Centre for Good Older Lives" and the Faculty of Science, University of Copenhagen for facilitating the symposium at the Frederiksberg campus.

Sammendrag

Nordisk samarbejde indenfor ernæringsområdet har en lang historie og inkluderer blandt andet udviklingen og opdateringer af de Nordiske Næringsstof Anbefalinger (NNR). Som en del af dette fortsatte arbejde og med finansiel støtte fra NKMT organiserede en nordisk projekt gruppe et symposium om den dobbelte risiko tilgang indenfor ernæringsområdet.

Formålet med symposiet var at diskutere den nuværende brug af og nogle af de udfordringer, der ligger i at benytte en dobbelt risiko tilgang, når man fastsætter næringsstofanbefalinger – set i lyset af den forestående opdatering af de NNR.

Som den første oplægsholder fastslog Inge Thorsdottir, IS, at konceptet med en dobbelt risiko tilgang indenfor ernæringsområdet stammede fra den potentielle risiko for et utilstrækkeligt indtag af næringsstoffer i den lave ende og et toksisk indtag af næringsstoffer i den høje ende af fordelingen af næringsstofindtag. Udviklingen af NNR igennem de sidste næsten 40 år afspejler den øgede opmærksomhed på, at et enkelt tal vedrørende gennemsnitligt næringsstofbehov ikke er tilstrækkeligt til at dække de forskellig behov for reference værdier, der både kan dække den lave og den høje ende af fordelingen af næringsstofindtag.

Inge Tetens, DK, gav et overblik over den terminologi, der benyttes i de nordiske næringsstofanbefalinger, der på mange måder er mangen til de termer, der benyttes i andre lande, regioner og internationale agenturer – dog med nogle væsentlige forskelle. NNR anvender ikke udtrykket Tilstrækkeligt Indtag (AI) men anvender et Lavere Indtags Niveau (LI), der defineres anderledes end i andre referenceværdier. Det blev understreget, at der er et stort behov for harmonisering af disse terminologier. Anna Karina Lindroos, SE, diskuterede brugen af LI værdier i en nordisk sammenhæng og gav eksempler fra en vurdering af utilstrækkeligt indtag af udvalgte mikronæringsstoffer ved at benytte LI som cut-off point og argumenterede, at værdien ikke behøves på populationsniveau. Jan Alexander, NO, gav en oversigt over tolerabelt øvre indtagsniveau (UL), som er det maksimale indtag af et kronisk dagligt indtag af et næringsstof, som vurderes at være utilbøjelig til at lede til bivirkninger hos mennesker. UL værdier fastlægges for at beskytte befolkningen imod bivirkninger fra for højt indtag af mikronæringsstoffer. Eksempler på, hvorledes UL værdier sættes, blev giver for selen og D-vitamin igennem deres biologiske bivirkninger i relation til et stigende indtag.

Som del af de udvalgte nuværende udfordringer indenfor den dobbelte risiko vurdering, der er særlig relevant for de nordiske lande, præsenterede Liisa Valsta, FI, data for brugen af kosttilskud, der er steget betydeligt indenfor de sidste par årtier i alle de nordiske lande. Sammenligninger mellem lande og bidraget af kosttilskud til det totale indtag af mikronæringsstoffer viste store forskelle mellem lande og indenfor lande. Lotte Høgberg, DK, gav en præsentation af et nyligt danske D-vitamin

forgiftningssituation blandt småbørn. Sagen demonstrerede et nationalt eksempel på en kollektiv risiko håndtering og illustrerede nogle af de lovgivningsmæssige udfordringer relateret til kosttilskud sammenlignet med registrerede lægemidler. Eksemplet demonstrerede ligeledes behovet for vel-etablerede kommunikationsveje imellem sundheds agenturer og sundhedssystemet.

Jod er et næringsstof, som har modtaget øget videnskabelig opmærksomhed i de nordiske lande efter et systematisk review under den seneste opdatering af NNR2012 viste, at jodstatus i de nordiske lande generelt ikke var vel-dokumenterede. Ingibjörg Gunnarsdottir, IS, og helle Margrethe Meltzer, NO, gav en oversigt over den nordiske situation og understregede, hvordan det nordiske samarbejde havde igangsat nye forsknings-aktiviteter with resultater, der viste, at mild jod mangel er til stede i forskellige befolkningsgrupper, herunder blandt gravide kvinder.

Mangel på data som grundlag for at sætte referenceværdier for næringsstoffer blev adresseret. Hildegard Przyrembel, DE, forklarede, at ekstrapolation fra en gruppe til en anden ofte anvendes i forbindelse med fastsættelse af reference værdier. Ekstrapolation kan foretages i forhold til kropsvægt eller i relation til energiforbrug, hhv. isometrisk (lineær) eller allometrisk skalering. Anvendelsen af begge metoder blev diskuteret i relation til næringsstoffer.

Nogle af de udfordringer, der er i forbindelse med at fastlægge referenceværdier for energi blev præsenteret af Monika Neuhaeuser-Berthold, DE. Trods variation i fysisk aktivitet varierer det daglige energiforbrug relativt lidt imellem individer, men varierer betydeligt imellem individer selv efter justering for krops-størrelse. En af de store udfordringer er at bestemme referenceværdier for energi for ældre personer, dels pga. mangel på data for energiforbrug ved hvile og dels for total energiforbrug blandt personer over 80 år. Ændringer i kropssammensætning med alderen er en særlig faktor, der kræver opmærksomhed og herunder at få kvantificeret den fysiske aktivitet, der er nødvendig for vedligeholdelse af muskelmasse.

Tommy Cederholm, SE, gav en oversigt over proteinanbefalingerne for de ældre i NNR2012, hvor sygdomme også blev benyttet som kriterier for fastsættelse af reference værdier. Han argumenterede, at et lavt proteinindtag bidrager til en utilstrækkelig muskel re-modellering og muskel-tab, hvilket igen kan føre til sarkopeni. For at forebygge en sådan udvikling blev proteinanbefalingerne i NNR2012 øget for de ældre personer fra 0.8 til 1-1.2 gram/kg kropsvægt/dag. Det blev understreget, at et højt proteinindtag kan have negative effekter på nyrefunktion for visse grupper med underliggende sygdomme.

Elizabeth Yetley, USA, gav et opsummering af, hvorledes komitéer, der var sammenbragt af det amerikanske Institut for Medicin, historisk havde benyttet en dobbelt risiko fastlæggelse tilgang til at fastlægge næringsstof reference værdier (DRI). I en nylig rapport blev der givet vejledende principper for, hvordan kroniske sygdomme vil kunne inddrages i fremtidige evalueringer af reference værdier, med nøglespørgsmål om, hvorvidt der er en kausal sammenhæng mellem næringsstoffer og kroniske sygdomme, og, hvis det er tilfældet, hvordan den kvantitative indtag-respons kurve ser ud.

Rune Blomhoff, NO, opsummerede sine indtryk fra dagen ved at udtrykke tilfredshed med det rettidige tidspunkt for afholdelsen af symposiet, da det adresserede emner, som er højst relevante for den forestående opgave med opdatering af de nordiske næringsstofanbefalinger. Han understregede behovet for harmonisering af terminologier og fremgangsmåde, de specielle nordiske udfordringer og de stimulerende tanker i relation til de tilgange, som benyttes for nærværende og de muligheder, der ligger for fremtiden.

I sine afsluttende bemærkninger takkede Inge Tetens for de mange fremragende præsentationer fra de inviterede eksperter og gode efterfølgende diskussioner. Hun udtrykte tillid til, at symposiet havde opfyldt dets formål – at bidrage til at styrke kapaciteten blandt de nordiske eksperter, der er involveret i den forestående opdatering af NNR og til at øge gennemsigtigheden i det dobbelte risiko vurdering tilgang indenfor ernæringsområdet.

Appendix I: Program

Wednesday 14 March 2018, Aud. A1-01.01, University of Copenhagen, Bulowsvej 17, Frederiksberg C, Denmark.

- 09:00–09:05: Welcome – *Inge Tetens, DK*.

Session one: The Dual Risk approach in Nutrition – The concept, terminologies and approaches. *Chairs: Helle Margrete Meltzer & Hanna Eneroth*.

- 09:05–09:15: Introduction to the Dual Risk concept in nutrition – *Inga Thorsdottir, IS*.
- 09:15–09:35: Terminologies in nutritional risk assessment – *Inge Tetens, DK*.
- 09:35–09:55: The approach and use of the lower level (LI) in the Nordic countries – can we do without it? – *Anna Karin Lindroos, SE*.
- 09:55–10:15: The approach in setting the upper level (UL) – methodologies and issues to address – *Jan Alexander, NO*.
- 10:15–10:25: What are the implications for NNR? Time for questions and reflections – *Moderators*.
- 10:25–10:50: Coffee break.

Session two: Current challenges. *Chairs: Inga Thorsdottir & Hanna Eneroth*.

- 10:50–11:10: What are nutrient intakes from supplements vs intakes from diets in the Nordic countries? – *Liisa Valsta, FI*.
- 11:10–11:30: Infants and vitamin D intoxication, recent outbreak in DK – *Lotte CG Høgberg, DK*.
- 11:30–11:50: Pregnancy/lactation and iodine, recent situation in Nordic countries – *Ingibjorg Gunnarsdottir, IS*.
- 11:50–12:00: What are the implications for NNR? Time for questions and reflections – *Moderators*.
- 12:00–13:00: Lunch.

Session three: Filling in the data gaps – extrapolations. *Chairs: Liisa Valsta & Inge Tetens.*

- 13:00–13:25: Extrapolations – allometric or isometric scaling? – *Hildegard Przymbel, DE*.

- 13:25–13:50: Challenges in setting reference values for energy – *Monika Neuhaeuser-Berthold, DE*.
- 13:50–14:15: Elderly and protein recommendation – when disease endpoints are also considered – *Tommy Cederholm, SE*.
- 14:15–14:30: What are the implications for NNR? Time for questions and reflections – *Moderators*.
- 14:30–14:55: Coffee break.

Session four: Where do we go from here. *Chairs: Liisa Valsta & Inge Tetens*.

- 14:55–15:20: Options for basing dual risk assessment on chronic disease endpoints – *Elizabeth Yetley, US*.
- 15:20–15:50: Symposium Panel discussion: How can we use the dual risk approach for the future NNR? Impressions of the day – *Rune Blomhoff, NO, chair of the upcoming NNR2022*, followed by a Panel discussion with presenters of the day! – *Moderators.*
- 15:50–16:00: Closing remarks – *Inge Tetens, DK*.

Appendix II: List of participants

Table 5: Participants at dual risk symposium March 14th, 2018

	Name	Affiliation
1	Aileen Robertson	Metropolitan University College, Copenhagen
2	Amanda Cramer-Nielsen	University of Copenhagen
3	Andrea Gutierrez	Metropolitan University College, Copenhagen
4	Ania Lopez	KU master student
5	Ann Bech Roskjær	University of Copenhagen, NEXS
6	Anna Karin Lindroos	Livsmedelsverket
7	Anne Marie Beck	Metropolitan University College, Copenhagen
8	Anne Marie Raabyemagle	University of Copenhagen, NEXS
9	Anne Scott	Fødevarestyrelsen
10	Astrid Lykke Pedersen	Metropolitan University College, Copenhagen
11	Birthe Kofoed Mortensen	Absalon University College, Sorø
12	Camilla Banke Birk	Albertslund Kommune
13	Caroline Noergaard	University of Copenhagen, NEXS
14	Cecilia Andersen	Student
15	Cecilie Elisabeth Leinum	Metropolitan University College, Copenhagen
16	Charlotte Mortensen	University of Copenhagen, NEXS
17	Christian Ritz	University of Copenhagen, NEXS
18	Christina Ovesen Søndergaard	Meal advisor
19	Elizabeth Yetley	National Institutes of Health, USA
20	Ellen Trolle	DTU Food
21	Ellen Tørsleff	DTU Food
22	Emily Sonestedt	Lund University, Sweden
23	Esther González Padilla	Lund University
24	Eva Warensjö Lemming	National Food Agency Sweden
25	Gitte Ravn-Haren	DTU Food
26	Golda Fania	University of Copenhagen, NEXS
27	Gregers Hummelmose	NKMT, Cordic Council of Ministers
28	Grith Møller	University of Copenhagen, NEXS
29	Hacer Tanrikulu	Metropolitan University College, Copenhagen
30	Hanna Eneroth	Livsmedelsverket
31	Hanne Hauger	University of Copenhagen, NEXS
32	Helle M. Meltzer	Folkehelseinstituttet, Norge
33	Hildegard Przyrembel	The Federal Institute for Risk Assessment, Germany
34	Ida Marie Grønborg	DTU Food
35	Inga Thorsdottir	University of Island
36	Inge Tetens	University of Copenhagen, Vitality Centre
37	Ingibjorg Gunnarsdottir	Landspitali, Island
38	Jan Alexander	Folkehelseinstituttet, Norge
39	Jeamie Mercado	University of Copenhagen, NEXS
40	Johanne Louise Arentoft	DTU Food
41	Kamilla Eriksen	University of Copenhagen, NEXS
42	Lakshmi Pradeepa Jayawardena	Metropolitan University College, Copenhagen
43	Liisa Valsta	National Institute for Health and Welfare, FI
44	Loa Kalledsøe	Hjerteforeningen
45	Lone Sørensen	University of Copenhagen, NEXS
46	Lotte Høgberg	Bispebjerg og Frederiksberg Hospital
47	Magritt Brustad	UIT The Arctic University of Norway
48	Maj-Britt S. Andersen	Pfizer
49	Maria Berg Roholt Mortensen	Metropolitan University College, Copenhagen
50	Maria Mejer Nielsen	University of Copenhagen, NEXS
51	Maria Wik Markhus	Institute of Marine Research, Bergen, Norway
52	Matilda Nordman	Master's student at KU
53	Michael Kristensen	Metropolitan University College, Copenhagen
54	Mikkel Tullin	University of Copenhagen, NEXS

	Name	Affiliation
55	Monika Neuhaeuser-Berthold	University of Giessen
56	Morten Gram Sell	Student
57	Morten Poulsen	DTU Food
58	Maarten Nauta	DTU Food
59	Nadia	Student
60	Pia Christensen	University of Copenhagen, NEXS
61	Pia Snitkjær	Absolon University College, Sorø
62	Quenia dos Santos	University of Copenhagen, FOOD
63	Rikke Andersen	DTU Food
64	Rikke Larsen	Metropolitan University College, Copenhagen
65	Rune Blomhoff	University of Oslo
66	Sandra Fisker Tomczyk	Fødevarestyrelsen
67	Sara Engel	University of Copenhagen, NEXS
68	Sarah John	Member of the Danish Nutrition Society
69	Sarah Johnson	University of Copenhagen, NEXS
70	Selma Reguez	graduate from SCIENCE/NEXS
71	Signe Loftager Okkels	University of Copenhagen, NEXS
72	Signe M. Jensen	University of Copenhagen, NEXS
73	Simon R. Schacht	University of Copenhagen, Vitality Centre
74	Sofie Errendal	Student
75	Steen Stender	University of Copenhagen, NEXS
76	Stina Ramne	Lund University
77	Stine Ludvig	Københavns Professionshøjskole
78	Sussanne Bügel	University of Copenhagen, NEXS
79	Thorhallue Ingi Halldorsson	University of Island
80	Tina Bowley	Student
81	Tine Buch-Andersen	University of Copenhagen, FOOD
82	Tommy Cederholm	Uppsala University
83	Ursula Schwab	University of Eastern Finland

Appendix III: List of abbreviations

A	Answer
AI	Adequate Intake
ALAT	Parathyroid hormone
AMDR	Acceptable macronutrient distribution range
ANR	Average nutrient requirement
AR	Average requirement
C	Comment
D-A-C-H	Germany - Austria - Switzerland
DHA	Danish Health Authority
DPIC	Danish Poisons Information Centre
DRI	Dietary reference intake
DRV	Dietary reference value
EAR	Estimated average requirement
FAO	Food and Agriculture Organization
FFQ	Food frequency questionnaire
FNB	Food and Nutrition Board
INL	Individual nutrient level
IoM	Institute of Medicine
LI	Lower intake level
LRNI	Lower reference nutrient intake
LTI	Lover threshold intake
NIV	Nutrient intake value
NNR	Nordic Nutrition Recommendations
PRI	Population reference intake
PTH	Parathyroid Hormone
Q	Question
RDA	Recommended dietary allowance
RI	Recommended intake
RI	Recommended intake range for macronutrients
RNI	Reference nutrient intake
UK	United Kingdom
UL	Upper intake level
UNL	Upper nutrient level
WHO	World Health Organization

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The Dual Risk Approach in Nutrition

This report summarizes a Nordic symposium on the current use and challenges in applying a dual risk assessment approach in the setting of nutrition recommendations. The symposium is timed with respect to the forthcoming update of the Nordic Nutrition Recommendations (NNR). At the symposium invited experts addressed the methodological framework for the dual risk approach for setting nutrition recommendations, including the terminologies and the criteria for the assessment. Case studies were presented to underline some of the specific current Nordic challenges, including use of supplements. Especially, the lack of data for risk assessment in nutrition was addressed with examples on extrapolations to subgroups such as children and the elderly and to energy and protein. Also, the development of nutrition risk assessment using nutrient intakes and chronic disease endpoints was addressed.

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